UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,635	05/18/2000	OLIVIER BALLEVRE	P00.0164	7617

29157 7590 10/23/2003

BELL, BOYD & LLOYD LLC
P. O. BOX 1135
CHICAGO, IL 60690-1135

EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 10/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/508,635	BALLEVRE ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 15 September 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see attached sheets*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached sheets*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *none*.

   Claim(s) rejected: *30,32,35 and 37-41*.

   Claim(s) withdrawn from consideration: *33 and 34*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

The amendment filed 9/15/03 directs the amendment of claims 30, 32, 35, 39-41. However, this amendment will not be entered. At the time of the final Office action (mailed 6/12/03), the invention was drawn to a method of using protein hydrolyzates or amino acids to promote recovery of an organ. The proteins were not limited to any particular source or amino acid sequence or even amino acid composition. In the proposed amendment, the invention is drawn to a method of using a "dietary milk hydrolyzate". First, a "milk hydrolyzate" would include the hydrolysis products of various compounds which occur in milk such as lipids. Sugars, amino acids, and trace metal ions (e.g., Fe, Cu, Cr, Mn) would also be included. There was no suggestion of any of this in the claims as presented during prosecution. But even if the claims were to be limited to a method of using hydrolyzates of proteins that occur naturally in milk, such claims would require a new search and examination to determine the novelty of using hydrolyzates of such proteins in the manner claimed.

Claims 30, 32-35 and 37-41 remain pending. Claims 33-34 remain withdrawn from consideration.

The claims were previously rejected as unpatentable over each of the following: Ballard (USP 5,679,771) in view of Duguay (*Journal of Biological Chemistry* 270 (29) 17566-74, 1995); Ballard (USP 5,679,771) in view of Wunderlich (USP 5,614,219); Mukai, Kiyoshi (JP- 3264525); Goldberg M. (*Horm. Metab. Res.* 12 (3), 94-96, 1980); Mawatari (USP

5,580,903) Henningfield (USP 5,221,668). In the response filed 9/15/03 it is argued that the proposed amendments to the claims overcome these rejections. However, the amendment is not being entered, and so the §103 rejections are maintained.

*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32, 35 and 37-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to teach a skilled physiologist how to use protein hydrolyzates and amino acids to promote "recovery" of an organ. As stated in Ex parte Forman (230 USPQ 546, 1986) and In re Wands (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

As for the "nature of the invention", it is asserted in the specification (page 8, line 17+)

that the disclosed protein hydrolyzates can be used to repair damage to the intestine. Also asserted (page 8, line 20+) is that the disclosed protein hydrolyzates can be used to treat Crohn's disease, diarrhea, colitis or sepsis, and further, that the disclosed protein hydrolyzates can be used to reverse damage to gut epithelial tissue that has resulted from a surgical procedure, or from any other cause. Though not specifically stated, the implication is that various diseases such as hepatitis, cirrhosis of the liver, and kidney infection can be successfully treated. Such diseases cause damage to organ tissue, and if the claimed method is to be effective, the protein hydrolyzates must be effective not only to accelerate wound healing, but overcome the pathological basis of the organ damage. As for the "working examples", the specification discloses results which are consistent with the conclusion that if one administers a mixture of all 20 genetically encoded amino acids to a mammal, the relative weights of the stomach, intestine, duodenum jejunum, liver, gastrocnemius, soleus, and extensor will vary slightly if the ratio of amino acids is altered. This assertion is somewhat suspect, since no statistical analysis has been presented. For example, in the case of the duodenum, the standard deviation would not have to be high at all in order to justify the conclusion that the results are not statistically significant. Without further information as to the variability in the data (that is presented on page 17), it is not particularly meaningful. The results are also not meaningful, since the amount of lipids and minerals (see page 14) were varied simultaneously with the amino acid composition. Furthermore, the total amount of amino acids varies from from feed mixture

to the next. Thus, even if it turns out that the results on page 17 are statistically significant, it has not been determined the extent to which, or even whether, the observed changes in organ weights were the result of varying the amino acid composition, rather than the lipids and minerals. It may be the case that the changes in organ weights were due to changes in the total amount of amino acids administered, rather than variations in the amino acid content. Or maybe the changes in organ weights were due to changes in differential metabolism of the peptide fragments which were produced by the different hydrolysis methods (hydrolyzate 1, hydrolyzate 2 or hydrolyzate 3). Thus, in the disclosed experiments (specification) several different variables have been altered simultaneously, and it is impossible to determine the effects of any one of them taken alone. Furthermore, there is no control experiment. It has not been stated what the results are supposed to be relative to. If the feed compositions (feed 1 - feed 5) were given to rats which were already exhibiting a positive nitrogen balance, would there be any effect at all of the different feeds?

Even if it turns out that the results on page 17 are statistically significant, and if could be determined what the cause (among the numerous variables) of the variance in organ weights might be, the results are still not meaningful with respect to the claimed invention. The claimed invention is not drawn to a method of randomly altering the weights of selected organs. And even if the claims were drawn e.g., to a method of increasing the weight of the stomach, it is not at all clear how one would proceed. It may be true that if one uses, e.g., feed #5 rather than feed #1, one will obtain a slightly higher weight of the stomach.

If it were to turn out that this difference is due to the amino acid content, rather than to the lipids and minerals (or one of the other variables), it would still not be evident how one would translate the results of feed #5 versus feed #1 into a general method of increasing stomach weight. It is not apparent which amino acids are necessary, or which are sufficient; it is not made clear wat degree of hydrolysis will produce the intended results, and which will not. And even if it were true that the specification taught the skilled artisan how to increase the weight of specific organs, there is no teaching as to how that teaching would translate into a showing of enablement for the claimed invention, which is that of using protein hydrolyzates and amino acids to promote "recovery" of an organ.

The results of a second experiment are presented on pages 21-24. What is shown here is that the rate of protein synthesis varies somewhat depending on which of the five feeds is used. The shortcomings of the experimental results described on page 17 apply here as well. First, the results are not statistically significant in the absence of further information as to the variability that is observed from one experiment to the next (for a given feed composition). Second, there are several different variables (with respect to the feed composition itself) which are altered simultaneously. And third, even if there were a clear assertion as to the specific variable that is supposed to correlate with the increased protein synthesis, and even if there were an experimental basis for such an assertion, this would have little relevance to the claimed invention, which is that of using protein hydrolyzates and amino acids to promote "recovery" of an organ. The specification has presented no

evidence that any such correlation exists between rate of protein synthesis, and recovery of an organ from wounding, physical trauma, or damage from an inflammatory condition. The reality is that one cannot "predict" such "recovery" based on rates of protein synthesis.

The following references discusses the issue of statistical analysis, and more importantly the issue of artifacts or invalid conclusions that can be drawn from an inadequate experimental design, or flawed assumption:

Ludbrook (*Clinical and Experimental Pharmacology and Physiology* 28 (5-6) 488-92, 2001)

Bryant (*Pediatric Allergy and Immunology* 9 (3) 108-15, 1998)

Bezeau (*Journal of Clinical and Experimental Neuropsychology* 23 (3) 399-406, 2001)

Bolton (*Journal of Clinical Pharmacology* 38 (5) 408-12, 1998)

Willenheimer (*Progress in Cardiovascular Diseases* 44 (3) 155-67, 2001)

Chung (*Plastic and Reconstructive Surgery* 109 (1) 1-6, 2002)

Atkinson (Chronobiology International 18 (6) 1041-53, 2001).

While several experiments have been conducted, there is no apparent relationship between the results of those experiments, and the claimed invention. The claimed invention encompasses repair of damage to the intestines, treatment of Crohn's disease, treatment of diarrhea, treatment of colitis or sepsis, treatment of hepatitis, treatment of cirrhosis of the liver, and kidney infection, as well as reversal of damage to gut epithelial tissue. There

is no evidence that increasing DNA synthesis or even increasing organ weight engenders a method of promoting wound healing, or of successfully treating a patient whose organs have been damaged by disease, surgery or trauma. "Undue experimentation" would be required to practice the claimed invention.

In response to the foregoing, it is argued (response, 9/15/03), that adequate direction is provided to enable the skilled artisan to prepare the "dietary protein" mixture to which the claims are drawn, but this does not address the issue raised in the previous Office action, which was how to "use" the "dietary protein" mixture.

Next, it is argued that the specification discloses a number of experiments which demonstrate the benefit of a dietary protein on the "growth or recovery of an organ". However, the claims are not drawn to a method of promoting "growth or recovery of an organ"; instead, the claims are drawn to a method of promoting recovery (only) of an organ.

It is also argued that the specification discloses that the composition of example 2 is effective to increase the weight of the intestines. However, the claims are not drawn to a method of increasing the weight of the intestines. Instead, the claims are drawn to a method of promoting the "recovery" of an organ.

Next, it is argued that, in comparing the effects of feed 2, 3, 4 and 5, one can see variability in the increase in weights of various organs. First, there is no indication of what the results are in comparison to. It appears that what the specification shows is that if rats are fed a diet of proteins, carbohydrates, lipids and minerals, a slight increase in the

weight of organs can be detected relative to what a rat would exhibit if it received no nutritional support at all. However, the claims are not drawn to a method of increasing the weight of organs in an animal relative to what would be observed in the absence of any nutrition. Nor are the claims drawn to a method of increasing the weight of organs in an animal in the absence of any benchmark. Instead, the claims are drawn to a method of promoting the "recovery" of an organ. It is also argued that the rate of protein synthesis is higher in the case of feeds 3-5 than in the case of feeds 1-2. First, the claims are not drawn to a method of increasing the rate of protein synthesis, and second, the claims (as amended by paper No. 24, filed 5/6/03) do not reflect any difference between feeds 3-5 (on the one hand) and feed 2 (on the other hand); both are encompassed.

Next, it is argued that the results are conclusive (for increasing weight of organs) since only the quantity and composition of proteins/hydrolyzates were varied to an extent that was "statistically relevant". However, the basis of this statement is not made clear. For example, the difference in mineral content in mineral content between feed 4 and feed 5 is far greater than the difference in protein concentrations between feeds 4 and 5; the same is also true in the case of feeds 4 and 1. But even if it were true that the quantities of the non-protein ingredients (carbohydrate, lipids, minerals, ash) were identical in all experiments, the results would still be inconclusive. This is true in part because, to the extent that variations in the weights of the organs is due to changes in peptide or amino acid composition of the "protein source", the claims do not reflect the differences in peptide or

amino acid composition that the response argues is signicant. For example, the response argues (page 5, filed 9/15/03) that the effect of feed 4 on the intestine is significantly different from that of feeds 2 and 3. Yet whatever may be the difference between feeds 2 and 3 (on the one hand) and feed 4 (on the other hand) is not reflected in the claims. For example, in the case of feed 4, the proportion of peptides having a molecular weight in the ranges of 200-1400 Daltons is far greater than is the case with feeds 1 or 2. Whatever the significance of this may be is not reflected in claim 30, for example. Claim 35 does require the presence of small peptides, however, if the objective of a physiologist were to increase the weight of the liver, for example, he would be well advised to avoid feed #4. Accordingly, since the organs are not specified, the skilled artisan would not know how to proceed if his objective were to increase the weight of organs. In any case, the claims are not drawn to a method of increasing the weight of organs; instead, they are drawn to a method of promoting the recovery of organs.

It is also argued that if the degree of hydrolysis of the protein source is in excess of 17%, the rate of protein synthesis is greater than if the degree of hydrolysis is below this number. However, the claims are not drawn to a method of increasing the protein synthesis rate; instead, they are drawn to a method of promoting the recovery of organs.

Next, it is asserted that if a compound is effective to increase the weight of an organ, and the protein synthesis rate within that organ, it follows that the compound will be effective to "promote recovery" of the organ. However, no basis is given for this assertion.

Based on the record thus far, there is no evidence from the prior art that a correlation exists between the propensity of a compound to increase the weight and protein synthesis rate within an organ (on the one hand), and the therapeutic efficacy of that compound in the treatment of diseases or disorders such as Crohn's disease, diarrhea, colitis or sepsis, hepatitis, cirrhosis of the liver, kidney infection, cardiac ischemia, inflammatory bowel disease, or to reverse damage to gut epithelial tissue that has resulted from a scission or blunt trauma. The "state of the art" is such that no correlation exists between the effects of a compound on weight and protein synthesis rate, and the therapeutic efficacy of the compound in achieving "recovery" of diseased or damaged tissue. Further, there are no "working examples" which show the skilled artisan how to use the recited protein hydrolyzates to treat any of the diseases listed above. There is also no guidance in the specification which directs the skilled artisan to undertake specific steps that will be effective to treat any of the diseases (listed above) using the protein hydrolyzates (to which the claims are drawn). In addition, there is no evidence that efficacy in an attempted treatment of the various inflammatory and infectious diseases (listed above) can be "predicted" based on the propensity of a compound to increase protein synthesis or to increase weight of an organ.

In accordance with the foregoing "undue experimentation" would be required to practice the claimed invention.

*

Claims 30, 32, 35 and 37-41 are rejected under 35 U.S.C. §112 second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The claims are drawn to a method of promoting "recovery" of an organ. It is unclear as to what the organ is recovering from. The the term could potentially encompass recovery from a wound, physical trauma, or a disease. In the response, it is argued (response filed 9/15/03) that the skilled artisan would be able to discern a few examples of what may be encompassed. However, the basis of this rejection is that the limits between what is encompassed and what is not encompassed are unclear. For example, one organ is the brain. Is "recovery" from a headache encompassed, or recovery from emotional stress, or recovery from excessive alcohol consumption? It is suggested that the claim be amended to make clear what the mammal is recovering from.

- Claim 30 recites the following:

  "...selecting a dietary protein selected from ... a protein hydrolysate... [and]...amino acids...".

  As noted previously, a "dietary protein" is not *per se* an amino acid. In the response filed 9/15/03, an amendment is proposed; it is asserted that this amendment would overcome the rejection if entered. However, the amendment is not being entered; the rejection is maintained.

*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 10/20/03

christopher S. F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600